Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the
Peripheral and Central Nervous System Drugs Advisory Committee Meeting
May 22, 2013

Location: The FDA White Oak Campus, Building 31, The Great Room (Rm. 1503), White Oak Conference Center, Silver Spring, Maryland.

Topic: The committee discussed new drug application (NDA) 204569, for suvorexant tablets, submitted by Merck Sharp and Dohme Corp, Worldwide Regulatory Group. The proposed indication is for insomnia characterized by difficulties with sleep onset and/or maintenance.

These summary minutes for the May 22, 2013, meeting of the Peripheral and Central Nervous System Drugs Advisory Committee of the Food and Drug Administration were approved on June 14, 2013.

I certify that I attended the May 22, 2013, meeting of the Peripheral and Central Nervous System Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/	***/s/***
Glendolynn S. Johnson, Pharm.D.	Paul B. Rosenberg, M.D.
Designated Federal Officer, PCNS	*Acting Chair, PCNS*

Summary Minutes of the Peripheral and Central Nervous System Drugs Advisory Committee Meeting
May 22, 2013

The following is the final report of the Peripheral and Central Nervous System Drugs Advisory Committee (PCNS) meeting held on May 22, 2013. A verbatim transcript will be available in approximately six weeks, sent to the Division of Neurology Products and posted on the FDA website at:
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/ucm346581.htm

All external requests for the meeting transcript should be submitted to the CDER Freedom of Information Office.

The Peripheral and Central Nervous System Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on May 22, 2013 at the FDA White Oak Campus, Building 31, The Great Room (Rm. 1503), White Oak Conference Center, Silver Spring, Maryland. Prior to the meeting, members and temporary voting members were provided copies of the briefing materials from the FDA and Merck Sharp and Dohme Corp., Worldwide Regulatory Group. The meeting was called to order by Paul B. Rosenberg, M.D. (Acting Chairperson); the conflict of interest statement was read into the record by Glendolynn S. Johnson, Pharm.D. (Designated Federal Officer). There were approximately 115 people in attendance. There were three Open Public Hearing speakers.

Issue: The committee discussed new drug application (NDA) 204569, for suvorexant tablets, submitted by Merck Sharp and Dohme Corp, Worldwide Regulatory Group. The proposed indication is for insomnia characterized by difficulties with sleep onset and/or maintenance.

Attendance:
PCNS Members Present (Voting): Emilia Bagiella, Ph.D; Robert R. Clancy, M.D.; Jeffrey A. Cohen, M.D.; Richard P. Hoffman, Pharm.D. (Consumer Representative); Michelle M. Mielke, Ph.D.; Paul B. Rosenberg, M.D. (Acting Chairperson); Jason W. Todd, M.D; Justin A. Zivin, M.D.

PCNS Members Not Present (Voting): Nathan B. Fountain, M.D.; Ellen J. Marder, M.D.

PCNS Member Present (Non-Voting): Lynn Kramer, M.D., FAAN (Industry Representative)

Temporary Members (Voting): Ronald D. Chervin, M.D., M.S.; Christian Guilleminault, D.M., M.D., DBiol; Daniel G. Morrow, Ph.D.; Natalie Compagni Portis, Psy.D (Patient Representative); Matthew Rizzo, M.D., FAAN; Roger R. Rosa, Ph.D.; Richard J. Ross, M.D., Ph.D.; Lisa M. Schwartz, M.D, M.S.; Robert B. Voas, Ph.D.

FDA Participants (**Non-Voting):** Ellis Unger, M.D.; Russell G. Katz, M.D.; Ronald Farkas, M.D., Ph.D.; Hristina Dimova, Ph.D.

Designated Federal Officer (Non-Voting): Glendolynn S. Johnson, Pharm.D.

Open Public Hearing Speakers: Diana Zuckerman Ph.D. (National Research Center for Women & Families); Sammy Almashat, M.D., M.P.H. (Health Research Group, Public Citizen); Russell Rosenberg, Ph.D. (National Sleep Foundation).

The agenda proceeded as follows:

Call to Order and Introduction of Committee	**Paul B. Rosenberg, M.D.** Acting Chairperson, PCNS
Conflict of Interest Statement	**Glendolynn S. Johnson, Pharm.D.** Designated Federal Officer, PCNS
FDA Introductory Remarks	**Russell Katz, M.D.** Director Division of Neurology Products (DNP) Office of Drug Evaluation I (ODE-I) Office of New Drugs (OND), CDER, FDA
SPONSOR PRESENTATIONS	**Merck Sharp and Dohme Corporation**
Introduction to Suvorexant	**Nadine Margaretten, Ph.D.** Senior Principle Liaison Global Regulatory Group Merck Research Laboratories
Insomnia Background, Suvorexant Clinical Development Overview, Methods and Results	**Wm. Joseph Herring, M.D., Ph.D.** Executive Director, Clinical Research Neuroscience and Ophthalmology Merck Research Laboratories
Suvorexant Dose Recommendations and Benefit/Risk Assessment	**David Michelson, M.D.** Vice President, Clinical Research Neuroscience and Ophthalmology Merck Research Laboratories
Clarifying Questions	
BREAK	
FDA PRESENTATION	
Suvorexant Safety and Efficacy	**Ronald Farkas, M.D., Ph.D.** Cross-Discipline Team Leader, DNP ODE-I, OND, CDER, FDA
Clarifying Questions	

LUNCH

Open Public Hearing

Questions to the Committee/Committee Discussion

BREAK

Questions to the Committee/Committee Discussion

ADJOURNMENT

Questions to the Committee:

Efficacy

1) For suvorexant, the applicant seeks an indication for the treatment of insomnia characterized by difficulties with sleep onset and/or maintenance. The proposed dosing algorithm includes higher and lower doses for non-elderly and elderly patient populations.

	non-elderly age < 65	elderly age ≥ 65
high dose	40 mg	30 mg
starting dose	20 mg	15 mg

a. **DISCUSSION:** Please discuss whether separate doses are necessary for non-elderly and elderly patient populations.

Committee Discussion*: The committee did not come to a consensus regarding whether separate doses are necessary for non-elderly and elderly patient populations. Some of the committee members agreed that the dosing should not be dependent on age (non-elderly versus elderly), but on other factors such as obesity, gender, etc., which may have an effect on appropriate dosing. Please see the transcript for details of the committee discussion.*

b. **DISCUSSION:** Please discuss separately the evidence of effectiveness in improving sleep onset and sleep maintenance

Committee Discussion: *Some of the committee members expressed concerns regarding the evidence of effectiveness for sleep onset, but the majority of the committee agreed that there was evidence of effectiveness for sleep maintenance. Please see the transcript for details of the committee discussion.*

c. *Based on the discussions that transpired, this question was revised to the following during the meeting:* **VOTE:** Are these dose ranges effective for the treatment of insomnia characterized by difficulties with sleep onset?

Vote: YES = 12 NO = 4 ABSTAIN = 1

Committee Discussion: *The majority of the committee agreed that the dose ranges are effective for the treatment of insomnia characterized by difficulties with sleep onset. The committee members who voted "NO" noted their decision was based on the lack of evidence for the low dose. The committee member who abstained noted that he does not have the clinical background to make a determination on effectiveness. Please see the transcript for details of the committee discussion.*

d. *Based on the discussions that transpired, the following question was added during the meeting:* **VOTE:** Are these dose ranges effective for the treatment of insomnia characterized by difficulties with sleep maintenance?

Vote: YES = 16 NO = 0 ABSTAIN = 1

Committee Discussion: *The majority of the committee agreed that the dose ranges are effective for the treatment of insomnia characterized by difficulties with sleep maintenance. The committee member who abstained noted that he does not have the clinical background to make a determination on effectiveness. Please see the transcript for details of the committee discussion.*

2) The applicant has submitted data supporting the conclusion that 10 mg is an effective dose. If 10 mg were the recommended initial dose, labeling would include a recommendation to increase the dose, if necessary, to achieve efficacy for an individual patient (if safety of higher doses were considered acceptable). Such labeling could reduce side effects and would be consistent with recent labeling changes for zolpidem products.

a. **DISCUSSION:** Please discuss the pros and cons of the general approach of starting sleep-aid drugs at the lowest dose with a reasonable effect, even if not the full effect.

Committee Discussion*: The committee agreed that starting at the lowest dose and titrating to a higher dose would be a soundapproach. However, some committee members stated a concern that starting with a dose too low could lead to patients taking a second dose in the middle of the night to get the desired effect, or feeling dissatisfied with the drug and/or prescriber. Please see the transcript for details of the committee discussion.*

b. **DISCUSSION:** Please discuss whether the applicant has established that 10 mg is an effective dose.

Committee Discussion*: Based on the data presented, the committee did not come to a consensus as to whether the applicant established that 10 mg is an effective dose. Please see the transcript for details of the committee discussion.*

c. **DISCUSSION:** Please discuss whether 10 mg would be an appropriate recommendation as a starting dose, with labeling that suggests increasing the dose for patients in whom 10 mg is not effective**.**

Committee Discussion*: The committee did not come to a consensus as to whether 10 mg would be an appropriate recommendation as a starting dose, with labeling that suggests increasing the dose for patients in whom 10 mg is not effective. Some committee members expressed that there was not enough evidence to suggest that the 10 mg dose was an effective dose and that phase 3 trials should be conducted to provide sufficient efficacy data. In contrast, other committee members concluded that 10 mg would be an appropriate recommendation as a starting dose because it allowed for more individualized therapy as patients could be titrated to the dose that was effective for them. Please see the transcript for details of the committee discussion.*

d. *Based on the discussions that transpired, this question was revised to the following during the meeting:* **VOTE**: Should the applicant be required to perform additional efficacy studies of the 10 mg dose prior to approval??

Vote: YES = 5 NO = 11 ABSTAIN = 1

Committee Discussion: *The majority of the committee agreed that the applicant should NOT be required to perform additional efficacy studies of the 10 mg dose prior to approval as an additional study would not provide new information. The committee members who voted "Yes" were concerned that the 10 mg dose is not an effective dose and additional efficacy studies should be performed by the sponsor prior to approval. Some of the committee members who voted "No" indicated that there is no efficacy at the 10 mg dose and thus there is no reason to further study this dose prior to approval. In contrast, other committee members who also voted "No" concluded that there is already enough evidence of efficacy at the 10 mg dose and therefore no additional efficacy studies should be required prior to approval. Please see the transcript for details of the committee discussion.*

3) **DISCUSSION:** The Agency believes that the safe use of hypnotic drugs should incorporate the concept that the lowest effective dose should be used. The exposure-response data suggests doses even lower than 10 mg might be effective in some patients. Please discuss whether the applicant should study safety and efficacy of doses lower than 10 mg

Based on the discussions that transpired, the committee did not address question #3.

Safety

4) **VOTE**: The applicant has recommended starting doses of 15 mg and 20 mg in elderly and non-elderly patients, respectively. Is the safety of these doses acceptable?

Vote: YES = 13 NO = 3 ABSTAIN = 1

Committee Discussion: *The majority of the committee agreed that the safety of these doses is acceptable. The committee members who voted "Yes" agreed that the observed adverse events at these doses are similar to those of currently approved drug products for insomnia. The committee members who voted "No" were concerned about the safety profile, potential drug interactions, and the potential for harm in the higher doses. It was noted that it would be reasonable to titrate patients to these doses as these doses are not safe starting doses. The committee member who abstained expressed concerns with non-neurologists prescribing this drug product without adequately assessing for co-morbidities. Please see the transcript for details of the committee discussion.*

5) **VOTE:** The applicant has recommended doses up to 30 and 40 mg in elderly and non-elderly patients, respectively, who have not responded to lower doses. Is the safety of these doses acceptable, if recommended only for patients who do not respond adequately to lower doses?

Vote: YES = 7 NO = 8 ABSTAIN = 2

Committee Discussion: *The committee did not come to a consensus as to the safety of doses up to 30 and 40 mg in elderly and non-elderly patients, respectively, who have not responded to lower doses. The committee members who voted "Yes" noted their concern of the lack of efficacy at the lower doses and that it would be appropriate to start low and monitor for side effects as the dose is titrated. The committee members who voted "No" noted that there is no evidence of increased efficacy at the higher doses but there is evidence of increased adverse events, such as somnolence, at the higher doses. The committee member who abstained noted that it is uncertain if this drug product at these doses is less safe than products currently on the market. Please see the transcript for details of the committee discussion.*

6) **DISCUSSION:** The Agency believes that in some populations (e.g., obese women; patients taking metabolic inhibitors) the 15 mg dose results in excessive suvorexant exposure. Please discuss if you agree.

Committee Discussion*: Several of the committee members agreed that the 15 mg dose in some populations (e.g., obese women; patients taking metabolic inhibitors) does not result in excessive suvorexant exposure, and that this is not a huge concern. Please see the transcript for details of the committee discussion.*

7) **DISCUSSION:** If you deem the safety of suvorexant to be acceptable at some dose(s), please discuss whether labeling could be adequate to protect patients who drive, and to protect the public? If so, what would need to be included in labeling?

Committee Discussion*: Individual committee members suggested the following be included in the labeling to protect patients who drive and to the public:*

- *Use plain language that is clear and easy to understand, especially for people with lower literacy skills*
- *Use protocols for supporting face to face physician and patient communication*
- *Recommend a 1 week follow up with the prescribing provider to assess safety and efficacy*

- *Request driving assessment self reports from the patient*
- *Include the following statements in the label "Do not use heavy machinery or drive a car" and "Do not use with alcohol".*
- *Include a warning about somnolence even if the patient is not feeling sleepy*

Please see the transcript for details of the committee discussion.

The meeting was adjourned at 5:00 p.m.